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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,219	06/29/2006	Claudia Scharer-Brodbeck	27656/41464	6786

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EXAMINER	
JOIKE, MICHELE K	
ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,219	SCHARER-BRODBECK, CLAUDIA	
	Examiner	Art Unit	
	Michele K. Joike	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-17 and 19-33* is/are pending in the application.

4a) Of the above claim(s) *19-21,29 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,13-17,22-28 and 31-33* is/are rejected.

7)☒ Claim(s) *11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 1, 2010 has been entered.

Claims 1-11, 13-17 and 19-33 are pending, with claims 1-11, 13-17, 22-28 and 31-33 under consideration. Any rejection of record in the previous Office Action, mailed June 10, 2009 that is not addressed in this action has been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 9, 10, 25 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 3, it is unclear how the first DNA sequence is replacing the second DNA sequence. In claim 1, the target vector already has the first DNA sequence present in it. In claim 2, an additional (second) DNA is present in the vector. How is the first DNA sequence replacing the second DNA sequence? In the specification there is discussion

of a first DNA sequence integrating into a DNA sequence already present in the vector, but this is not what is being claimed.

In claim 9, the first DNA sequence replaces a CDR region. However, the claim is dependent on claim 8 which refers to the second DNA sequence. Should the DNA sequence in claim 9 be the "second DNA sequence" or is the first DNA sequence in claim 9 replacing the second DNA sequence, which is a CDR region, in claim 8?

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 13-17, 24, 27, 31 and 32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Meinhardt et al in view of Butler et al, and in further view of US 6,410,271. This rejection is maintained for reasons of record. Claim 8 is added. The second sequence (interpreted as an additional sequence since the vector further comprises a second sequence) encodes an antibody. As taught by US 6,410,271, genes (more than one) encoding antibodies and regions of antibodies can be present in the vectors, and great efforts have made to mimic such a natural maturation of antibodies against various antigens, especially antigens associated with diseases such as autoimmune diseases, cancer, AIDS and asthma.

Claims 22 and 23 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Meinhardt et al, Butler et al and US 6,410,271 as applied to claims 1-8, 13-17, 24, 27, 31 and 32 above, and further in view of Monschau et al. This rejection is maintained for reasons of record.

Claims 28 and 33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Meinhardt et al, Butler et al and US 6,410,271 as applied to claims 1-8, 13-17, 24, 27, 31 and 32 above, and further in view of Jirholt et al. This rejection is maintained for reasons of record.

Response to Arguments Concerning Claim Rejections – 35 USC § 103 (a)

Applicant's arguments filed February 1, 2010 have been fully considered but they are not persuasive.

The following grounds of traversal are presented:

None of the art teaches use of the gamma toxin gene as a negative selection marker, or cell lines susceptible to gamma toxin effects for homologous recombination. They all teach use of positive selection markers, and switching to negative selections markers is contradictory. In particular, Meinhardt teaches that the selection markers are the donor sequences and integrated into the target sequence, not the target DNA sequence. Also, the method in Meinhardt is typically not useful for generating a randomized library with the use of selection markers as donor sequences. Lastly, Meinhardt uses cells that are resistant to gamma toxin gene effects.

Butler does not teach that gamma toxin is useful as a negative selection marker which is removed by homologous recombination. It also does not teach making a randomized gene library.

US 6,410,271 does not teach a useful negative selection system using gamma toxin as the negative selection marker for constructing a randomized library.

The references teach away from the claimed invention because they teach use of positive selection markers. Meinhardt teaches use of a positive selection marker that relates to homologous recombination in the cytoplasm, and not the nucleus. Butler identified mutants that were resistant to gamma toxin induced G1 arrest. Therefore, one of ordinary skill in the art would not have been motivated to use Butler because the plasmid can lose its growth arrest ability, which would lead to inconsistent selection.

The combination of Meinhardt and Butler lead to inoperability because homologous recombination in these cells would lead to expression of the gamma toxin in toxin-sensitive cells, leading to cell death.

The specification provides unexpected results because the method described significantly reduces background clones and improves cloning efficiency. The cited references did not recognize that background is a problem in random library generation.

Applicant's arguments have not been found persuasive for the following reasons.

In the claims, the gamma toxin has been replaced by a donor sequence. In Meinhardt, integration of the LEU2 and *aph* genes disrupts the killer toxin. Therefore the procedure of having the killer toxin disrupted by integration is the same. See figure

1. Butler is the reference that teaches the gamma toxin as a negative selection marker, and use of cells that are susceptible to gamma toxin. The method using homologous recombination for integration to disrupt a killer toxin is taught by Meinhardt, as discussed above. US 6,410,271 is the reference that teaches a method for generating highly diverse libraries of expression vectors encoding fusion proteins, such as single-chain antibodies, via homologous recombination in yeast. Combined, they teach the claimed method.

Butler teaches that gamma toxin can cause G1 arrest in cells. It teaches that when cells sensitive to gamma toxin were transformed with a plasmid encoding the gamma toxin gene, these cells were unable to form colonies. This is negative selection. Therefore, Butler teaches that gamma toxin can be used as a negative selection marker. The combined references do not lead to inoperability because Meinhardt teaches integration of genes to disrupt the killer toxin. Therefore, there would be no expression of the gamma toxin.

The references do not teach away. As discussed, Butler teaches gamma toxin can act as a negative selection marker. Spontaneously arising mutants that were toxin-resistant were also noted. However, spontaneously arising mutations is a common phenomenon, and does not rise to the level of teaching away.

While significantly reducing background clones (false positives) and improves cloning efficiency is an improvement, it does not rise to the level of being unexpected. The problem of false positives was contemplated by US 6,410,271 (see description of

figures 4 and 7). The reference teaches that pre-screening can aid in eliminating false positives, as well as other means. Eliminating false positives was a goal.

Allowable Subject Matter

Claim 11 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele K. Joike whose telephone number is (571)272-5915. The examiner can normally be reached on M-F, 10:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michele K. Joike/
Primary Examiner, Art Unit 1636

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